Phase II Efficacy Results using an Oncolytic Herpes Simplex Virus (NV1020) in Patients with Colorectal Cancer Metastatic to the Liver (mCRC)

S. K. Geevhargese[1], A Chen[2], D. A. Geller[3], H. A. de Haan[2], A. Iagaru[4], A. Knoll[5], J. Nemunaitis[6], T. R. Reid[7], D. Sze[4], K. Tanabe[8]

[1]Vanderbilt University, Nashville, TN; [2]Clinical Research Dept, MediGene Inc, San Diego, CA; [3]University of Pittsburgh, Pittsburgh, PA; [4]Stanford University, Palo Alto, CA; [5]Clinical Development, MediGene AG, Martinsried, Germany; [6]Mary Crowley Medical Research Center, Dallas, TX; [7]University of California San Diego, CA; [8]Harvard Medical School, Boston, MA

Background

- Oncolytic viruses have shown potential as effective new anticancer agents.[1,2]
- NV1020 is a modified, replication-competent Herpes simplex virus with marked antitumor activity in animal models.[3] Additive effects have been observed when combined with conventional chemotherapy in rodents.
- Optimal Biological Dose for intrahepatic artery infusions was established in initial clinical Phase I studies (single[4,5] & multiple[6] doses).

Study Design (Figure 1)

- Open-label, fixed dose (optimal biological dose) preliminary Phase II study (n = 22).
- Inclusion criteria: HSV-1 seropositive, failed 1st/2nd line mCRC chemotherapy, tumor progression with liver-dominant metastases on ^{18}F FDG PET/CT scans.
- Four, weekly NV1020 1X10^8 pfu infusions administered via transfemoral catheter into hepatic artery.
- NV1020 was followed by a minimum of two cycles of additional conventional chemotherapy.
- Tumor response was evaluated post NV1020, after 2 cycles of chemotherapy, and 3-monthly for 12 months. Efficacy was determined by blinded, independent radiology panel, using modified RECIST (CT) and EORTC (SUV_{max} PET). Indefinite periodic telephone follow-up determined long-term safety and survival.

Median Age (Range)	60 years (33, 79)
Male/ Female	73% / 27%
KPS ≥ 90	96%
Time since primary CRC resection (Median, Range)	18.8 months (5.0, 51.1)
Median CEA (Range)	23.8 ng/ml (1.7-2808)
Prior mCRC chemotherapy	5FU-based regimen: 100% FOLFOX: 77% FOLFIRI: 58% FOLFOX+FOLIRI 50% Targeted agents: 86% Radiofrequency ablation: 29%

Table 1: Patient Baseline Characteristics

Results

- 18 (82%) patients completed full treatment as scheduled; only 2 (9%) discontinued NV1020 prematurely (after 2 infusions) due to tumor progression and rapidly fatal clinical decline. Two (9%) refused both cycles of post NV1020 chemotherapy due to personal reasons.
- Post NV1020 chemotherapy comprised only drugs to which 45% patients were previously refractory to. Only one new agent was administered to 36% patients.

Clinical Safety (NV1020 - related)

- Post infusion febrile reaction was the most common adverse event (91% patients)
  - Maximum 104°F (Grade 2), duration 6 – 24 hours.
  - Associated with rigors (59%), myalgia (50%), headache (45%) and fatigue (36%).
  - Effectively managed with antipyretics and analgesia.
- Other common Grade 1/2 events were nausea (55%), vomiting (36%).
- Grade 3 toxicity: Lymphopenia in two patients (10%) (occurrence after initial infusion of NV1020; asymptomatic, transient (<7 days), not treated, subsequent infusions were associated with Grade 1 lymphopenia).
- No NV1020-related serious adverse events were reported at any time.
- No NV1020 shedding was ever detected (PCR analysis of serum, saliva or genital swabs) for up to 14 days post NV1020 infusion.

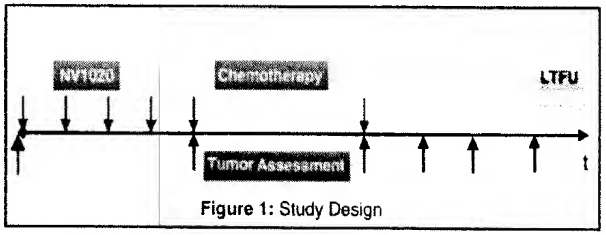

Figure 1: Study Design

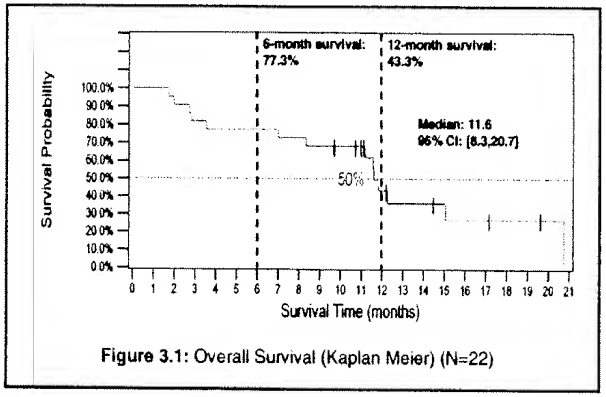

Figure 3.1: Overall Survival (Kaplan Meier) (N=22)

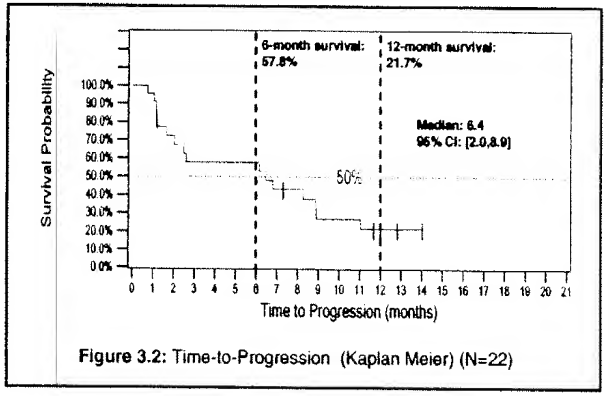

Figure 3.2: Time-to-Progression (Kaplan Meier) (N=22)

Abstract 4088, Poster Board H14
Date: Sunday, May 31, 2009, Time: 8:00 AM - 12:00 PM
Location: Orange County Convention Center, Level 2, West Hall C, Orlando, FL

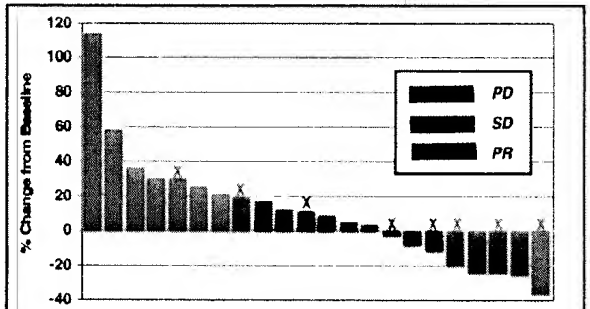

Figure 3.3: Waterfall Plot of Best Overall Response (N=22) (X=alive)

Efficacy (Figures 3.1, 3.2 and 3.3):

- After NV1020 alone 50.0% (11/22) had stable disease on CT compared to 36.4% (8/22) on PET.
- After chemotherapy 68.8% (11/16) had non-progressive disease on CT, whereas 81.3% (13/16) on PET.
- Best Clinical Response: 15/22 (68.2%) had clinical response on CT (14 SD, 1 PR), on PET there were 16/22 (72.7%) clinical responder (9 SD, 7 PR).
- Median Survival was 11.6 months (95% CI [8.3,20.7]) and median Time-to-Progression 6.4 months (95% CI [2.0,8.9]).
- 12-month Survival Rate came to 43.3%, Time-to-Progression Rate to 21.7%.
- Despite intrahepatic delivery of NV1020, some remote responses were observed.
- Response showed no correlation with initial tumor size, SUV or CEA, nor with time since primary resection, nor with pre- or post NV1020 chemotherapy type.

Conclusions

1. Repeated intrahepatic infusions of 1x10^8 pfu NV1020 were remarkably well tolerated.
   i) Cytokine-mediated viral reaction is transient, mild and easily managed with antipyretics/analgesia.
   ii) Consistent, asymptomatic, immunological effects (neutralizing antibody, HSV-2 seroconversion) were observed.
   iii) Virus delivery was well accepted by investigators and patients.
2. No adverse interactions were reported with follow-up chemotherapeutic agents.
3. NV1020 stabilizes liver metastases in highly advanced, refractory mCRC and may sensitize tumors to salvage chemotherapy and extend survival.
4. A controlled Phase II/III controlled trial is now justified.

References:

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EXHIBIT F